REMARKS

Reconsideration of this application, as amended, is respectfully requested.

The Examiner made the restriction requirement final and withdrew nonelected Claims 8-14 from consideration in this patent application. In response, the present amendment confirms the withdrawn status of the nonelected Claims 8-14.

It is not clear why the Examiner did not consider the information disclosure statements filed December 12, 2000 and August 2, 2001. Both statements complied with the statutory requirements in that they provided a copy of Form PTO-1449 or a similar substitute form listing the patents or publications that had been submitted to the Office for consideration (see the attached true copies of the forms listing the documents for consideration) and indicate that they supplied a copy of each document (see the attached true copies of the relevant assertions and the postcards showing receipt of the complete information disclosure statements by the Office). It cannot readily be determined, therefore, what is missing from either statement since they both appear to be complete. Applicants would be happy to comply with the Examiner's requirement if they are apprised of the exact nature of the problem. If the Office has misplaced all of the proffered documents, for instance, the Examiner is invited to contact the undersigned attorney to request another set.

It is respectfully requested that the Examiner explain in more detail what must be done for consideration of the documents or consider the two information disclosure statements in the Official record. If the Examiner will kindly consider the citations, a duplicate copy of three pages of forms listing the patents and publications is provided herewith for his convenience. Applicants respectfully ask that the Examiner consider the listed items, initial each form, return a copy thereof to Applicants with the next communication and enter the original form into the application file.

The Examiner rejects Claims 1-3 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement due to the terms "bioresponse modifier" and "cytokine inducer" for reasons set forth in the Office action on pages 3 and 4. To expedite matters, Applicants have omitted the term "bioresponse modifier" from Claim 1 but respectfully contest the rejection as it applies to the preferred embodiment of the present invention relating to the specific term "cytokine inducer."

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The amended method of Claim 1 comprises the use of a combination of a cytokine inducer and a chemotherapeutic agent in accordance with the teaching in the application on page 2, lines 25-32. The written description provides a thorough definition of the cytokine inducer of the present invention as referring to those agents that induce cytokine production and listing quite a few examples such as IL-1, TNF, muramyl dipeptide, lipopolysaccaride, beta-glucan and the synthetic cytokine inducers disclosed in U.S. Patent Nos. 5,312,831 and 4,666,890. One of ordinary skill in the art would appreciate the strong correlation among the examples of the natural and synthetic cytokine inducers based on the same mode of action or function to induce cytokine production by stimulating the immune system to produce an inflammatory response mediated by cytokines. The application adequately describes the invention in no uncertain terms to indicate a well-defined scope of the claimed method that includes the use of the compounds of formula I or other cytokine inducers that are comparable in biological activity to the compounds of formula I.

The Examiner also rejects Claims 1-7 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement due to the term "treating solid tumor" for reasons set forth in the Office action on page 4. Applicants respectfully traverse this rejection.

Applicants believe that the illustration of the claimed method in the non-small cell type lung cancer ("NSCLC") cell line H-157 sufficiently correlates to other solid tumors. The fact that the H-157 cell line grows in nude mice strongly implies that it is representative of growing human tumors in that not every tumor line will grow in nude mice. Therefore, the H-157 line is very useful as a solid tumor model. Also, the remarkable chemotherapy activity of the cytokine inducers is not directed at the tumor itself. Rather, it is directed at the host (mouse or human) response to the tumor. The evidence for this conclusion is that the formula I compounds do not inhibit tumor cell growth in tissue culture (see page 7, lines 3-6, of the application).

Furthermore, it is well known that chemotherapeutic agents such as docetaxel, doxorubicin and the like that are often selected to combat NSCLC can also be employed in combination therapies to treat other solid tumors such as metastatic breast cancer, stomach cancer, sarcomas, *etc.* All of these solid tumors are highly fatal and are in desperate need for new therapies to improve the patient's survival rate. Nevertheless, if an agent is found to be useful against the non-small cell lung solid tumor, it will be reasonable to use the agent against other solid tumors such as head and neck, stomach, pancreatic, cervical, melanoma, adrenal cortex, soft

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tissue sarcomas and the like (see page 1, lines 21-29, and page 8, lines 14-16, of the application). In other words, a solid tumor model comprising the NSCLC cell line H-157 is an acceptable means for investigating the efficacy of the claim-recited combination against a broad range of solid tumors. Hence, the exemplification of the invention in the NSCLC cell line H-157 and the clinical trials fully support the breadth of the term "treating solid tumor."

In view of the amendment and the foregoing comments, it is respectfully requested that the Examiner withdraw the rejections of the claims under 35 U.S.C. § 112, first paragraph.

The Examiner rejects Claims 1-7 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Ayral-Kaloustian *et al.* (U.S. Patent No. 5,545,662) in view of The Merck Index. Applicants note but respectfully traverse the Examiner's rejection set forth on pages 5 and 6 of the Office action.

With all due respect, it is believed that the Examiner has misread the '662 patent by taking the true prior use of the compounds of formula I out of context. The '662 patent does disclose that the formula I compounds are useful in cancer treatment but it definitely does not teach or imply that the compounds may find use as chemotherapeutic agents. There is a huge distinction of how the compounds would have been used in the medical field and what the oncologist would have expected from administration of the compounds based on the '662 patent in comparison to the present teachings. The examples of the patent clearly show that the compounds of formula I are useful as adjuvants to chemotherapy by restoring bone marrow function after chemotherapy and by ameliorating the neutropenia effect caused by the anticancer treatment. There is absolutely no teaching or suggestion in the reference that the compounds of formula I can be used as anticancer agents themselves or even that they possess any anticancer properties to suggest combining them with other anticancer agents for purposes of treating solid tumors.

In point of fact, the opposite is true. Applicants have demonstrated that the claim-recited compounds of formula I are totally devoid of anticancer activity; they did not inhibit tumor cell growth in nude mice or in tissue culture (see page 7, lines 1-6, of the application). In view of the absence of anticancer activity, it is surprising that the claimed combination of the cytokine inducer and the chemotherapeutic agent would have synergistic activity against H-157 (see the excellent results in Table 1 on page 6 of the application). The clinical trial with cancer patients also shows unforeseen potency of the novel chemotherapy treatment against late stage disease. The complete

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response rate with the combined therapy of paclitaxel and carboplatin is roughly only 5% but when the representative compound of formula I is added to the therapy, the cancer patients have an unexpected, significantly enhanced benefit in complete response (3 out of 6 patients), partial reduction in tumor mass (1 out of 6 patients) or stabilization of disease (1 out of 6 patients).

Since the compounds of formula I are not taught by the art to be useful for the same purpose as anticancer agents in treating solid tumors, it is not *prima facie* obvious to combine the two ingredients and expect enhanced chemotherapeutic efficacy. The fact that the compounds of formula I or any other cytokine inducer are devoid of anticancer activity would negate any motivation for the skilled artisan to combine the two pharmaceuticals for the claim-designated purpose. Therefore, the unanticipated synergism of the combination is persuasive evidence to prove that the claimed method for treating solid tumors is unique and patentable.

Moreover, there is a long-standing need in the art to find chemotherapeutic strategies that work successfully against highly fatal, solid tumors. The present invention solves the long-standing problem and significantly improves the survival rate by the unique administration of the combination of a cytokine inducer and a chemotherapeutic agent to treat solid tumors.

The Examiner has kindly provided alternative methods on page 7 for overcoming the rejection under 35 U.S.C. § 103(a). Since it will be appreciated that the '662 patent does not disclose the prior use of the compounds of formula I to treat solid tumors and does not constitute prior art under 35 U.S.C. § 102(e), the Examiner can find sufficient justification to withdraw the rejection based on Applicants' current response. Similarly, the rejection of Claims 1-7 under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over Claims 1 and 2 of U.S. Patent No. 5,545,662 in view of The Merck Index is rendered moot, as there is no real basis in fact to maintain the rejection. The methods of increasing neutrophil counts or accelerating neutrophil recovery to combat the negative side effects of cancer chemotherapy do not propose a method of treating solid tumors. One method does not suggest the other. They are independent and distinct methods that achieve totally different end results. In sum, the present invention is not rendered obvious by the art.

In view of the foregoing comments, it is respectfully requested that the Examiner withdraw the rejection of the claims under 35 U.S.C. § 103(a) and hold the application allowable.

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On a separate matter pertinent to this case, it is again respectfully asked that the Office kindly change the Attorney Docket Number on future correspondence to AM100081.01.

Accordingly, this application is now in condition for an allowance and such favorable treatment is respectfully urged.

Respectfully submitted,

WYETH

Date: December 31, 2003

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This correspondence is being deposited with the U.S. Postal Service on December 31, 2003 to be delivered by the "Express Mail Post Office to Addressee" service under Mailing Label Number EU730354195US addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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APPENDIX

AMENDMENTS TO THE CLAIMS

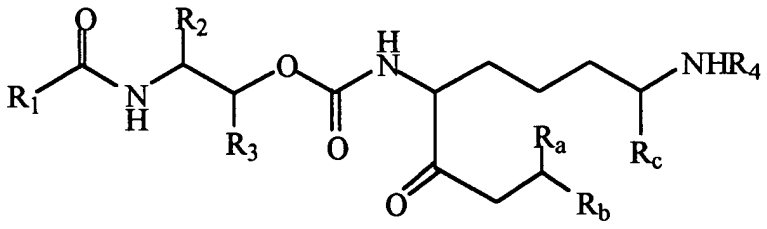
Please amend the claims as follows:

1 (Currently amended). A method of treating solid tumor in a mammal which comprises administering to said mammal an effective amount of a combination of a ~~bioresponse modifier~~ cytokine inducer and a chemotherapeutic agent.

2 (Cancelled).

3 (Currently amended). The method according to claim ~~2~~ 1, wherein the chemotherapeutic agent is a microtubular agent or a macrophage activating agent.

4 (Currently amended). The method according to claim 3, wherein the cytokine inducer is a compound of formula I, having the structure



I

wherein

R_1 is selected from the group consisting of hydrogen, a substituted or unsubstituted (C_1-C_{20}) alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted cycloalkylalkyl group, a vinyl group, an acetylene group, a substituted or unsubstituted amino group, a substituted or unsubstituted acylamino group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkylgroup, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted alkoxyaryl group, a substituted or unsubstituted alkoxyaralkyl group and a substituted or unsubstituted monocyclic or bicyclic heterocyclic group containing from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

R_a and R_3 are independently selected from ~~the group consisting of~~ hydrogen, substituted or unsubstituted (C_1-C_6) alkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkoxyaralkyl, vinyl, acetylene and a ~~sustituted~~ substituted or unsubstituted monocyclic or bicyclic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of nitrogen, sulfur and oxygen atoms provided that, in the case of R_3, the hetero atoms in said heterocycle are not directly bonded to the --CH-- group of the --CH--X-- moiety;

R_2, R_b and R_c are independently selected from ~~the group consisting of~~ carboxy or protected carboxy, ~~carboxy or~~ protected carboxyloweralkyl and carboxyamide;

X is oxygen or nitrogen;

R_4 is H or an amino protecting group; wherein the substituents in the aforementioned substituted alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, aryl, aralkyl, aryloxy, alkoxyaryl, alkoxyaryalkyl and heterocyclic groups are selected from the group consisting of halogen, hydroxyl, lower alkyl, lower alkoxy, aryloxy, aralkyloxy, amino, mono- or di-loweralkylamino, arylamino, aralkylamino, carboxyl, formyl, lower alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, loweralkylthio, arylthio, aralkylthio, arylsulfinyl, arylsulfinyl, aralkylsulfinyl, lower alkylsulfonyl, arylsulfonyl, aralkylsulfonyl and a monocyclic or bicyclic heterocyclic group having 1-4 hetero atoms selected from nitrogen, sulfur and oxygen;

or a pharmaceutically acceptable salt thereof.

5 (Original). The method according to claim 4, in which the compound of formula I is [R-(R*,R*)]-N-[(R)-6-carboxy-N^2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof.

6 (Currently amended). The method according to claim 5 wherein the microtubular agent or ~~macrphage~~ macrophage activating agent is selected from the group consisting of paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, ~~adriamycin, doxirubicin~~ doxorubicin, cisplatin, carboplatin, mitomycin C, and bleomycin.

7 (Currently amended). The method according to claim 6, wherein the microtubular agent or macrophage activating ~~agent agents are~~ is paclitaxcel, ~~and~~ carboplatin ~~or a combination thereof~~.

8 (Withdrawn).

9 (Withdrawn).

10 (Withdrawn).

11 (Withdrawn).

12 (Withdrawn).

13 (Withdrawn).

14 (Withdrawn).